REMARKS

In the Response filed with the RCE on November 15, 2002, Claims 16-19 were cancelled without prejudice and new Claims 22 and 23 were added. Thus, Claims 1, 4-9, and 13-15, 20-23 were pending. Applicant appreciates the Examiner's statement that Claim 1 is in condition for allowance and Claims 6-9 would be allowable if re-written to overcome the objections/rejections under 35 U.S.C. §112, second paragraph. Applicant is somewhat confused by the Examiner's conclusion that Claims 22 and 23 are withdrawn from consideration. These Claims simply explicitly claim the composition of matter (sequences) that are incorporated as elements of the other Claims. There was no restriction of the sequences in the Restriction Requirement dated March 22, 2001. Applicant respectfully submits that he is entitled to Claims that are directed toward the nucleic acid and amino acid sequences of CP-1, as recited in the Claims.

The Examiner has indicated that the title of the invention is not descriptive. Applicant appreciates the Examiner's suggestion for amending the title and have amended the title as suggested.

The Examiner has also objected to Claim 9, due to the presence of a typographical omission of a comma between "mutases" and "transferases." Applicant has amended the Claim to correct this error. Applicant notes that the Examiner has withdrawn the objection to the term "wpr" in the Claims.

Although various rejections have been withdrawn, in the present Office Action, the Examiner has set forth new grounds of rejection. The Examiner's rejections are addressed in the order listed below:

1) Claims 6-9, 13, 15, 20 and 21 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite;

2) Claims 13, 15, 20 and 21 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement;

3) Claims 13, 15, 20 and 21 stand 21 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not meeting the enablement requirement; and

4) Claims 13, 15, 20 and 21 stand rejected under 35 U.S.C. §102(b), as being anticipated by U.S. Patent No. 5,264,366 to Ferrari.

1) The Claims Are Definite

The Examiner has rejected Claims 6-9, 13, 15, 20 and 21, under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner indicates that there is insufficient antecedent basis for the recitation of "said microorganism" in Claims 6-9. Applicant has amended the Claims to recite "said *Bacillus subtilis*," as suggested by the Examiner. Thus, Applicant submits that these Claims are in condition for allowance.

In regard to Claims 13 and 15, the Examiner indicates that the Claims are unclear due to inconsistent use of terms. Applicant has amended the Claims to consistently recite "*Bacillus subtilis*," in order to ensure that there is no confusion regarding the Claim elements. In addition, in regard to Claims 13 and 20, the Examiner indicates that the Claims are confusing in the recitation of "at least one of the genes encoding *B. subtilis* cysteine protease 1, wherein said at least one of the genes" in claim 13 and "at least one of the genes encoding cysteine protease 1" in claim 20." (Office Action, page 3-4). Applicant has amended the Claims to more clearly recite the claimed elements. Thus, Applicant submits that these Claims are in condition for allowance.

2) The Present Specification and Claims Meet the Written Description Requirement

The Examiner has rejected Claims 13, 15, 20 and 21 under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement. In particular, the Examiner argues that the function of the mutant genes has not allegedly been adequately described in the Specification. Although the Examiner admits that the Claims are drawn to methods of using *B. subtilis* host cells comprising the mutant genes and not the mutant genes themselves, the Examiner argues that the "mutant genes are an essential element of the claimed invention and should be adequately described in the specification. The specification does not contain any disclosure of the function of all mutant nucleic acids as encompassed by the recited genera." (Office Action, page 4). Applicant must respectfully disagree, as those of skill in the art understand the functions of the proteins recited in the Claims. As indicated, inactivation of the CP1 (as well as CP2 and/or CP3) activity can be used in combination with deletions or mutations in other

proteases, such as apr, npr, epr, wpr, and mpr. (*See*, Specification, at page 2, lines 30-35; and page 9, lines 3-10). Indeed, on page 9 (lines 5-10), Applicant lists various patents and publications known to those in the art that describe mutations in these protease genes. As these mutants are known in the art, there is no requirement that Applicant provide a detailed description of the claimed embodiments. Indeed,

> "It is not necessary that the application describe the claim limitations exactly, . . . but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations.
> *In re Wertheim*, 191 USPQ 90, 96 (CCPA 1976).

Thus, Applicant respectfully submits that the combination of the inactive CP1 and mutant proteases is supported by the Specification as filed. Applicant respectfully submits that the Claims meet the written description requirement and requests that this rejection be withdrawn.

3) The Claims Meet the Enablement Requirement

The Examiner has rejected Claims 13, 15, 20 and 21, under 35 U.S.C. §112, first paragraph, as allegedly meeting the enablement requirement.

Applicant must respectfully disagree with the Examiner's above rationale and arguments. However, Applicant agrees with the Examiner's statement that the presently claimed invention provides ". . .a method for the production of a heterologous protein in a transformed *B. subtilis* host cell using a *B. subtilis* host cell comprising a gene encoding SEQ ID NO:2 or the nucleic acid of SEQ ID NO:1 with a mutation or deletion that results in the inactivation of CP1 activity." (Office Action, page 6). The Examiner also admits that the Specification is "enabling for a method for the production of a heterologous protein in a transformed B. subtilis host cell using a B. subtilis host cell comprising a gene encoding SEQ ID NO:2 or the nucleic acid of SEQ ID NO:1 with a mutation or deletion that results in the inactivation of CP1 activity . . . ." (Office Action, page 5). The Examiner argues that undue experimentation would be required to make and use the claimed invention. Applicant must respectfully disagree. Applicant submits that *any* mutation or deletion that results in the inactivation of CP1 proteolytic activity alone, or in combination with mutations or deletions in apr, npr, epr, wpr, and/or mpr is intended. Applicant is not required to provide each and every mutation or deletion that

would result in inactivation. The Specification as filed provides means to identify CP1, as well as the nucleic acid and amino acid sequences of CP1, and means to assess proteolytic activity (*See*, pages 5-9 and 12). The additional proteins are known in the art (*See e.g.*,page 9).

Nonetheless, in order to further the prosecution of the present application and Applicant's business interests, yet without acquiescing to the Examiner's arguments, Applicant has amended Claim 13 to explicitly recite a *B. subtilis* host cell comprising a nucleic acid encoding a heterologous protein wherein a mutation or deletion in the gene sequence of B. subtilis CP1 which results in CP1 inactivity. As the Specification as filed provides methods for identifying CP1 nucleic acids and polypeptides, as well as to assess CP1 proteolytic activity, Applicant submits that there is more than sufficient teaching in the Specification to enable the presently claimed invention. Furthermore, there is support in the Specification for the combination of CP1 inactivity with mutations in other proteases. Thus, Applicant respectfully submits that the Claims are allowable and requests that this rejection be withdrawn.

4) The Claims are Novel

The Examiner has presented a new rejection of Claims 13, 15, 20 and 21 under 35 U.S.C. §102(b) as being allegedly anticipated by U.S. Patent 5,264,366 to Ferrari *et al.* ("Ferrari"). The Examiner argues that "[a]s the mutant genes of the recited *B. subtilis* host cell can encode any protein, the host cell can essentially be any transformed *B. subtilis* host cell." (Office Action, page 8). Applicant must respectfully disagree, as the claimed invention involves host cells that have mutations and/or deletions in the CP1 gene such that the CP1 protein is inactive. Thus, contrary to the Examiner's argument, the host cell *cannot* be essentially any transformed *B. subtilis* host cell.

In order to anticipate the Claims, the Ferrari patent must teach each and every element of the claimed invention. As indicated above, the Claims have been amended without prejudice to recite that the CP1 is inactive. However, Ferrari provides no teaching of the claimed invention involving SEQ ID NO:2 and the inactivity of CP1. As Ferrari does not teach each and every element of the Claims[2], a requirement for a

[2] "Anticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention." *RCA Corp. v. Applied Digital Data Sys., Inc.*, 730 F.2d 1440, 221 USPQ 385, 388 (Fed. Cir. 1984).

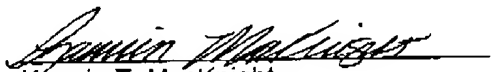
reference to be anticipatory, this patent does NOT anticipate the Claims. Applicant respectfully requests that this rejection be withdrawn and the Claims passed to allowance.

CONCLUSION

All grounds of rejection and objection of the Office Action of December 19, 2002, having been addressed, reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned.

Respectfully submitted,

Dated: March 12, 2003



Kamrin T. MacKnight
Registration No. 38,230

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304-1013
Phone: (650) 846-5838
Facsimile: (650) 845-6504

APPENDIX I

MARKED-UP VERSION OF SPECIFICATION'S REPLACEMENT PARAGRAPHS AND REWRITTEN, ADDED, AND/OR CANCELLED CLAIMS

The following is a marked-up version of the Specification's replacement paragraphs pursuant to 37 C.F.R. §1.121(b), as well as a marked-up version of the claims pursuant to 37 C.F.R. §1.121 (c)(1)(ii) with instructions and markings showing changes made herein to the previous version of record of the specification and claims. Underlining denotes added text while bracketing and quotes denote deleted text.

IN THE TITLE:

Please replace the title:

"Gram-Positive Microorganisms with Inactivated Cysteine Protease-1"

with the following new title:

Bacillus subtilis with an Inactivated Cysteine Protease-1

IN THE CLAIMS:

Please amend the Claims as follows:

6. (Thrice Amended) The *Bacillus subtilis* of Claim 1, wherein said [microorganism] *Bacillus subtilis* is capable of expressing a heterologous protein.

7. (Twice Amended) The [microorganism] *Bacillus subtilis* of Claim 6, wherein said heterologous protein is selected from the group consisting of hormones, enzymes, growth factors, and cytokines.

8. (Amended) The [microorganism] *Bacillus subtilis* of Claim 7 wherein said heterologous protein is an enzyme.

9. (Twice Amended) The [microorganism] *Bacillus subtilis* of Claim 8 wherein said enzyme is selected from the group consisting of proteases, carbohydrases,

lipases, isomerases, racemases, epimerases, tautomerases, mutases, transferases, kinases and phosphatases.

13. (Five Times Amended) A method for the production of a heterologous protein in a transformed *Bacillus subtilis* host cell comprising the steps of:

(a) obtaining a *Bacillus subtilis* host cell comprising a nucleic acid encoding said heterologous protein wherein said host cell contains a mutation or deletion in [at least one of] the gene[s] encoding *B. subtilis* cysteine protease 1, wherein said [at least one of the] gene[s] encoding cysteine protease 1 encodes the amino acid sequence set forth in SEQ ID NO:2, and said *B. subtilis* cysteine protease 1 is inactive; and

(b) growing said *Bacillus subtilis* host cell under conditions suitable for the expression of said heterologous protein.

15. (Twice Amended) The method of Claim 13 wherein said *Bacillus subtilis* host cell further comprises a mutation or deletion in at least one of the genes encoding at least one protease selected from the group consisting of apr protease, npr protease, epr protease, wpr protease and mpr protease.

20. (Twice Amended) The method of Claim 13, wherein said [at least one of the] gene[s] encoding cysteine protease 1 comprises the nucleic acid sequence set forth in SEQ ID NO:1.